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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/094,921	06/15/98	LINDHOFER	H 80309

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EXAMINER	
HOLLERAN, A	
ART UNIT	**PAPER NUMBER**
1642	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/094,921	Lindhofer et al
Examiner	**Group Art Unit**
Anne Holleran	1642

☒ Responsive to communication(s) filed on *Nov. 28, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-8 and 12-30* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8 and 12-30* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

DETAILED ACTION

1. This Office Action is responsive to the Amendment filed November 28, 2000.

Claims 9-11 were canceled.

Claims 27-30 were added.

Claims 1-8 and 12 -30 are pending and examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 1-8 and 12-27 are examined on the merits to the extent the claims read on methods using bispecific antibodies which are specific for CD3 (see election of species requirement). The election of species with regard to isotype combinations is withdrawn.

Claim Rejections Withdrawn:

4. The rejection of claims 23 and 24 under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101, is withdrawn in view of the amendment.

5. The rejection of Claim 24 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn upon further consideration of the claimed subject matter.

6. The rejection of Claims 9-11 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment canceling claims 9-11.

7. The rejection of claim 11 under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S. Patent 5,911,987; published 5,911,987; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; published Nov. 17, 1998; files June 7, 1996) is withdrawn in view of the amendment canceling claim 11.

Claim Rejections Maintained and New Grounds of Rejection:

8. The rejection of Claims 1-8 and 12-26 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained. New grounds of rejection are presented. Claims 27-28 are also rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to

particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it is not clear if in step "c" the tumor cells may be incubated with more than one type of antibody. If Applicant intends only one antibody then amendment of the recitation "and/or" to read "or" is required.

Claim 1 is vague and indefinite because of the phrase "the bispecific antibodies are members selected from the group consisting of the following isotype combinations". The term "bispecific antibody" is a reference to an antibody with two binding specificities whereas the members of the Markush group are isotype combinations.

Claim 1 is vague and indefinite because many of the "isotype combinations" listed as members of the Markush group include recitations describing parts of an antibody molecule other than an Fc portion of an antibody.

Claim 1 is vague and indefinite because it is not clear what product is modified the term "heterologous". First, are both the bispecific and trispecific antibodies heterologous? Second, is there such a thing as a non-heterologous bispecific or trispecific antibody?

Claim 1 is vague and indefinite because it is drawn to a method for making a vaccine product but does not include a step or a description of the product made.

Claim 13 is vague and indefinite because "the antibody-tumor cell preparation containing vaccine" lacks antecedent basis. This rejection would be obviated by amending the claim to read "preparing a vaccine comprising an antibody-tumor cell preparation.".

Claim 14 is vague and indefinite because it is not clear how "step c)" may be changed from what it is in claim 1, from which claim 14 depends. An additional step should be included.

Claims 17 and 18 are vague and indefinite because "said mononucleated peripheral cells" lacks antecedent basis.

Claims 23 and 26 are vague and indefinite because it is not clear what is encompassed by the "tumor cell preparation". Claims 23 and 26 depend from claim 1 which does not include a step or description of the product made.

Claim 27 is vague and indefinite because the isotype combinations lack antecedent basis in claim 1.

Claims 29 and 30 are vague and indefinite because the phrase "said mononucleated peripheral blood cells" lacks antecedent basis in claim 27 or claim 1.

9. The objection to the specification because it relies on a reference to subject matter disclosed within a claim is maintained. Although, amendment to page 3, lines 8-11 removed a reference to claim 1, the specification also contains a second reference to claim 1, specifically, page 20, line 21. Amendment of the specification to delete this reference is required. Applicant is advised to review the specification for further instances of references to claims within the disclosure of the specification.

10. The rejection of Claim 23 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained for the reasons of record. Applicant has provided no arguments to explain why this rejection should be withdrawn.

Claim 23 is drawn to methods of prevention of tumorous diseases as well as to methods of treatment. Thus, claim 23 can be interpreted as drawn to methods for the prevention of cancer. Because the method requires the use of bispecific or trispecific antibodies which are specific for tumor antigens, and because a method of prevention implies that the cancer has not occurred yet, it is not possible to understand how Applicant will know which antibodies to use. Moreover, because one of the steps of the claimed method requires the isolation of autologous tumor cells, it is not clear how Applicant may perform the claimed method in an individual who does not yet have cancer. Thus, the specification provides no teachings that would allow one of skill in the art to understand that Applicant was in possession of a method for the prevention of cancer.

11. The rejection of claims 14, 17 and 18 under 35 U.S.C. 102(b) as being anticipated by Honsik et al (U.S. Patent 4,844,893; published July 4, 1989) is maintained for claims 14, 17 and 18 and further applied to claims 28-30.

Applicant has not presented arguments as to why this rejection should be withdrawn. Claim 14 depends from claim 1 which has been amended to include limitations of isotype

combinations of bispecific antibody compositions or conjugates. The limitations do not apply to trispecific antibodies which are interpreted to be the functional equivalent of bispecific antibodies having an Fc portion. Thus, claim 14 can be interpreted to encompass methods which utilize antibodies preparations with only one type of Fc.

Honsik et al teach a method of using bispecific antibodies for the preparation of ADCC competent peripheral blood mononuclear cells comprising incubating peripheral blood mononuclear cells with bispecific antibodies which bind to the Fc receptor, to a tumor cell antigen and also bind to T-cells. The peripheral blood mononuclear cells are then mixed with tumor cells. Thus, Honsik et al teach a method of making a cellular vaccine against cancer cells that is the same as that of claims 14, 17 and 18.

12. The rejection of claims 1- 8, 12, 13, 15, 16 and 19-26 under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S. Patent 5,911,987; published 5,911,987; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; published Nov. 17, 1998; files June 7, 1996) is maintained and also applied to claim 27.

Claim 1 is interpreted to be drawn to a method of making a vaccine composition comprising isolated autologous tumor cells, treating the tumor cells to prevent survival and incubating the treated tumor cells with bispecific or trispecific antibodies which bind to a T cell, bind to at least one antigen on a tumor cell and bind to the Fc receptor of Fc receptor-positive cells. Claim 2 specifies the Fc receptor as the Fcγ receptor, I, II or III. Claim 3 specifies that the

antibodies bind to monocytes, macrophages, dendritic cells, natural killer cell or activated neutrophils by the Fcγ receptor I. Claim 4 specifies that the antibodies are capable of inducing tumor-reactive complement-binding antibodies. Claim 5 adds that limitation that antibodies be specific for CD3. Claim 6 adds the limitation that the antibodies elicit the CD40, CD80, CD86, ICAM-1 or LFA-3 antigens or the secretion of cytokines by Fc-receptor positive cells. Claim 7 adds the limitation that the cytokines secreted be IL-1, IL-2, IL-4, IL-6, IL-8, IL-12 or TNFα. Claim 8 adds the limitation that the bispecific antibody contains an anti-CD3 and an anti-tumor-associated antigen specificity. Claim 11 appears to have the same scope as that of claim 1. Claim 12 adds the limitation that the trispecific antibody contains an anti-CD3 and an anti-tumor-associated antigen specificity. Claim 13 adds a further step to the method, that of a short-term incubation step. Claims 15 and 16 specify the duration of the incubation period. Claim 19 adds the limitation that the amount of tumor cells used in the method is 10^7 to 10^9 cells. Claim 20 adds the limitation that the bispecific or trispecific antibodies be added in an amount of 2-100 ug. Claim 21 specifies that the cell treatment procedure is limited to irradiation. Claim 22 adds the limitation that the bispecific or trispecific antibodies are capable of activating the Fc receptor positive cells. Claim 25 appears to be of the same scope as that of claim 1.

Claims 23 and 24 are interpreted to be drawn to method of treatment of cancer comprising injecting the vaccine preparations of claim 1. Claim 26 is drawn to a pharmaceutical composition that is prepared by the method of claim 1.

Volker et al teaches a method of preparing a cellular vaccine from autologous tumor cells by isolating the tumor cells, freezing and thawing the isolated tumor cells (assumed to inactivate the tumor cells), infecting the tumor cells with Newcastle Disease Virus to antigenize the tumor cells and incubating the tumor cells with a bispecific cell bonding reagent which has a specificity for a Newcastle Disease Virus antigen and has a specificity for a T-cell (column 6, lines 58 - column 8, lines 13). The amount of tumor cells used to prepare the vaccine is 10^7 cells. The incubation step with the bispecific cell bonding reagent lasts for 30 minutes. The cells may be treated with 200 Gy radiation. The bispecific cell bonding reagent may have specificity for CD3. The cell bonding reagents may be made up of antibodies or fragments of antibodies. Volker et al also include a step of injecting the cellular vaccine preparation intradermally using a 0.9x40ml cannula.

Volker et al does not teach a bispecific or trispecific antibody (or cell bonding reagent) that has a specificity for a Fc receptor. However, the usefulness of using bispecific antibodies comprising an anti-Fc receptor specificity in the treatment of cancer is well known in the art as taught by Deo et al (see column 11, lines 11-16). Deo et al also teaches that the Fc receptor-specific antibodies are useful for binding to Fc receptor bearing cells such as monocytes, macrophages, neutrophils and dendritic cells which are cells that are involved in specific killing of target cells and presenting antigens to the immune system (column 6, lines 13-18). Deo et al also teaches that the Fc receptor-specific antibodies are useful for presenting antigen to antigen presenting cells of a patient (column 9, lines 20-30). Deo et al disclose a specific embodiment of

a bispecific antibody, H22, which contains an anti-FcγI receptor (FcγRI, see column 17, lines 60-67) and which possess ADCC activity mediated through FcγRI binding . Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the cell vaccine preparation method of Volker et al to include a cell bonding reagent that had an Fc receptor specific region, either in the form of an Fc receptor portion of an antibody or a region that would be specific for an Fc receptor. One of ordinary skill in the art would have been motivated to alter the vaccine preparation method of Volker et al to include antibodies with an Fc receptor binding specificity because of the teachings of Deo et al concerning the importance of the Fc receptor in the recruitment and stimulation of Fc receptor containing cells which would result in improved antigen presentation to the immune system.

13. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Volker et al (U.S. Patent 5,911,987; published 5,911,987; 102(e) date Feb. 21, 1997) in view of Deo et al (U.S. Patent 5,837,243; published Nov. 17, 1998; files June 7, 1996) and further in view of Lindhofer et al (Lindhofer, H. et al. J. Immunology, 155: 219-225, 1995).

The invention of claim 27 has been discussed above with respect to methods which read on methods using trispecific antibodies with no specification of isotype. However, the claimed inventions may also be interpreted as reading on methods drawn to methods using bispecific antibodies having a combination isotype of either rat-IgG2b/mouse-IgG2a, rat-IgG2b/mouse-IgG2b or rat-IgG2b/mouse-IgG3. Neither Volker et al or Deo et al teach making vaccine

preparations using combination isotype bispecific antibodies. However, Lindhofer et al teaches that rat/mouse combinations made from using the quadroma technique result in a higher yield of functional bispecific antibodies and also teach that a rat mouse combination isotype is easier to purify (see pages 219 -221 and Figure 1). Thus, it would have been prima facie obvious to one of ordinary skill in the art to have combined the teachings of Volker et al with that of Deo et al and Lindhofer et al to have made the claimed invention. One would have been motivated to have combined the teachings of Lindhofer et al with that of Volker et al and Deo et al because Lindhofer teaches the advantages of using rat/mouse combinations in purification of bispecific antibodies and in generating high yields of usable antibody product.

14. Claims 1-8, 12-26 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement commensurate with the scope of the claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-26 and 28 are drawn to methods of preparing a vaccine for treatment subjects with cancer, methods for treating cancer with the vaccine and drawn to compositions comprising the vaccine preparation. The methods comprise using bispecific antibodies of various types of combination isotypes. The methods may also comprise using trispecific antibodies which have a binding specificity toward an Fc receptor. The scope of the claimed methods where the methods

are drawn to using bispecific antibodies of various combination isotypes is not fully enabled by the disclosure of the specification.

Factors to be considered in determining whether undue experimentation would be required to make and use the claimed inventions are: 1) quantity of experimentation necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See Ex parte Forman, 230 USPQ 546, BPAI, 1986.

The specification provides little guidance concerning how to use the various bispecific antibodies having a combination isotype. The working example provided does not indicate whether the exemplified bispecific antibody has a combination isotype and if it does have a combination isotype, what the combination is.

The state of the art with regard to bispecific antibody isotype combinations is that only the rat/mouse isotype combination appears to be known (Lindhofer et al, supra). The use of combination istoype bispecific antibodies does not appear to be well established in the art so that one of skill in the art would know how to use any of the combinations recited in claim 1. The art of making bispecific antibodies also appears to be unpredictable with regard to quadroma technology, and while there is an example of successful isolation of rat/mouse combinations, Lindhofer also teaches that human IgG1/human IgG3 quadromas did not provide a high yield of usable bispecific antibody (see page 224, 2nd column).

Because the term bispecific antibody reads on antibodies made by methods other than the quadroma technique, such as conjugation of two intact monoclonal antibodies, the claimed methods read broadly on methods using products with either a hybrid Fc region or a product with two Fc regions. It is not clear from the specification that a combination isotype of an antibody with a hybrid Fc region would be able to crosslink an Fc receptor or that a conjugated bispecific antibody would be able to bind an Fc receptor. As the specification provides little guidance on how to make and use a representative number of usable combination isotypes and because the art provides very little teachings concerning the utility of bispecific antibodies having a combination isotype and whether such bispecific antibodies bind and crosslink Fc receptors, and because the art of making therapeutically useful bispecific antibodies is unpredictable, is not clear that one of skill in the art would be able to practice the claimed inventions where they read on using bispecific antibodies having the isotype combinations listed in claim 1.

Conclusion

No claim is allowed. This rejection contains new grounds of rejection and is not made final.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Anne Holleran, Ph.D. whose telephone number is (703) 308-8892. Examiner Holleran can normally be reached Monday through Friday, 9:00 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached at (703) 308-3995.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist at telephone number (703) 308-0196.

ALH

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February 26, 2001

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